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Current models, challenges and best practices for work conducted between European academic cooperative groups and industry

Stahel, Rolf A ; Lacombe, Denis ; Cardoso, Fatima ; Casali, Paolo G ; Negrouk, Anastassia ; Marais, Richard ; Hiltbrunner, Anita ; Vyas, Malvika

Abstract: BACKGROUND The academia-industry interface is important, and, despite challenges that inevitably occur, bears the potential for positive synergies to emerge. Perceived barriers to wider collaboration in academia-industry oncology research in Europe need to be addressed, current academic cooperative group and industry models for collaboration need to be discussed, and a common terminology to facilitate understanding of both sectors' concerns needs to be established with an eye towards improving academia-industry partnerships on clinical trials for the benefit of patients with cancer. **METHODOLOGY** CAREFOR (Clinical Academic Cancer Research Forum), a multi-stakeholder platform formed to improve the direction for academic clinical trials in the field of oncology in Europe, formed the CAREFOR-Industry Working Group comprised of experienced professionals from European academic cooperative groups joined by industry representatives selected based on their activities in the area of medical oncology. They jointly discussed academic cooperative groups, clinical trials conducted between academic cooperative groups and industry, examples of successful collaborative models, common legal negotiation points in clinical trial contracts, data access, and principles of interaction. **RESULTS** Four principles of interaction between the academia and industry are proposed: (1) clarify the roles and responsibilities of all partners involved in the study, (2) involve legal teams from an early stage; (3) acknowledge that data is an important output of the study, (4) agree on the intent of the trial prior to its start. **CONCLUSIONS** The CAREFOR-Industry Working Group describes current models, challenges, and effective strategies for academia-industry research in Europe with an eye towards improving academia-industry partnerships on clinical trials for patients with cancer. Current perceived challenges are explained, and future opportunities/recommendations for improvement are described for the areas of most significant impact. Challenges are addressed from both the academic and industry perspectives, and principles of interaction for the optimal alignment between academia and industry in selected areas are proposed.

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Current models, challenges and best practices for work conducted between European academic cooperative groups and industry

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ABSTRACT

Background The academia-industry interface is important, and, despite challenges that inevitably occur, bears the potential for positive synergies to emerge. Perceived barriers to wider collaboration in academia-industry oncology research in Europe need to be addressed, current academic cooperative group and industry models for collaboration need to be discussed, and a common terminology to facilitate understanding of both sectors' concerns needs to be established with an eye towards improving academia-industry partnerships on clinical trials for the benefit of patients with cancer.

Methodology CAREFOR (Clinical Academic Cancer Research Forum), a multi-stakeholder platform formed to improve the direction for academic clinical trials in the field of oncology in Europe, formed the CAREFOR-Industry Working Group comprised of experienced professionals from European academic cooperative groups joined by industry representatives selected based on their activities in the area of medical oncology. They jointly discussed academic cooperative groups, clinical trials conducted between academic cooperative groups and industry, examples of successful collaborative models, common legal negotiation points in clinical trial contracts, data access, and principles of interaction.

Results Four principles of interaction between the academia and industry are proposed: (1) clarify the roles and responsibilities of all partners involved in the study, (2) involve legal teams from an early stage; (3) acknowledge that data is an important output of the study, (4) agree on the intent of the trial prior to its start.

Conclusions The CAREFOR-Industry Working Group describes current models, challenges, and effective strategies for academia-industry research in Europe with an eye towards improving academia-industry partnerships on clinical trials for patients with cancer. Current perceived challenges are explained, and future opportunities/recommendations for improvement are described for the areas of most significant impact. Challenges are addressed from both the academic and industry perspectives, and principles of interaction for the optimal alignment between academia and industry in selected areas are proposed.

Key questions

What is already known about this subject?

- ▶ The academia-industry interface is important, and, despite challenges that inevitably occur, bears the potential for greatly positive synergies to emerge.
- ▶ There are perceived barriers to wider collaboration in academia/industry oncology research in Europe.
- ▶ The types of clinical trials conducted between industry and academia include Industry Sponsored Clinical Trials and Investigator Initiated Trials.

What does this paper add?

- ▶ There is a need to examine, discuss and either clarify or improve on the way academia-industry research is being conducted.
- ▶ There are several drivers for change in academia-industry collaboration: collaboration and exchange of knowledge, streamlined contracting and agreements, bidirectional exchange of knowledge and exchange of samples and technology.
- ▶ The value of the collaboration can be maximised by focussing on strengths and mutual areas of interest, crafting a collaboration model and contract that is fit for the given purpose and focussing on programmes that provide meaningful scientific patient-centric advances that go beyond only competitive considerations.

How might this impact on clinical practice?

- ▶ Principles of interaction between academia and industry were developed, and these provide guidance towards creating a clear and successful collaboration provided that the clinical trials performed capture data of sufficient quality. Patients with cancer are the ultimate beneficiaries.

INTRODUCTION

The academia-industry interface is important, and, despite challenges that inevitably occur, bears the potential for greatly positive synergies to emerge.

CAREFOR (Clinical Academic Cancer Research Forum), a multi-stakeholder

platform formed to improve the direction for academic clinical trials in the field of oncology in Europe,¹ includes the European Society for Medical Oncology (ESMO), the European Organisation for Research and Treatment of Cancer (EORTC), the European Association for Cancer Research (EACR) and is joined by European and international cooperative groups, umbrella organisations, medical societies, national cooperative groups and cancer centres in an effort to institutionalise academic cancer clinical research in the European landscape and, notably, structure collaboration with industry. CAREFOR formed the CAREFOR-Industry Working Group which comprises experienced professionals from European academic cooperative groups joined by selected industry representatives. The industry representatives were selected based on their activities in the area of medical oncology and their presence at the ESMO Congresses. In this paper, the CAREFOR-Industry Working Group identifies:

1. General Categories of Academic Cooperative Groups in Europe;
2. Types of Clinical Trials Conducted between Academic Cooperative Groups and Industry;
3. Examples of Successful Collaborative Models for Academia-Industry Clinical Trials;
4. Current Challenges for Academia Clinical Trials in Europe;
5. Common Legal Negotiation Points in Contracts for Clinical Trials between Academic Cooperative Groups and Industry;
6. Data Access and Management Models to Govern the Flow of Information and Data between Academia and Industry;
7. Emerging Collaborative Models;
8. Principles of Interaction between Academia and Industry.

The article seeks to address perceived barriers to wider collaboration in academia/industry oncology research in Europe by discussing current academic cooperative group and industry models for collaboration and establishing a common terminology to facilitate understanding of both sectors' concerns with an eye towards improving academia-industry partnerships on clinical trials for the benefit of patients with cancer. The challenges are addressed from both the academic and industry perspectives, and best practices, the optimal alignment between academia and industry in selected areas, are proposed throughout the article.

For purposes of clarity, when we discuss academic partnerships with industry, we are *not* referring to academic partnerships between a large hospital and the pharmaceutical industry, but rather to partnerships between industry and large established European academic groups whose membership is voluntary and comprise tens to hundreds of hospitals and institutions, that is, collectives coming from either one or multiple countries in the case of national and international academic cooperative groups. In this light and concerning terminology and definitions, the variety of academic groups

are introduced based on their geographic membership, capabilities and expertise. Common definitions are provided for clinical trials conducted by academia and clinical trials conducted by industry. Snapshots of collaborative models are provided, all the while keeping in mind the expectations, capabilities and resources of the involved partners. With this approach, the CAREFOR-Industry Working Group aims to shine a light on the current issues and outline best practices that might serve to mitigate perceived challenges for academic research within Europe.

It is noted, that further discussion on these areas may be warranted with stakeholders outside of the CAREFOR-Industry Working Group in order for this effort to have the utmost impact on improving the current state of affairs.

GENERAL CATEGORIES OF ACADEMIC COOPERATIVE GROUPS IN EUROPE

The landscape of academic cooperative groups in Europe comprises different categories of groups occupying specific niches in cancer clinical research. An overview of the categories and niches of academic groups is warranted, because the collaboration model with industry needs to fit with the resources and expertise of the respective category of academic group and the regulations it must adhere to within its membership's geography. For purposes of this overview, we consider three general categories of academic cooperative groups (see [table 1](#)):

1. Small Academic Cooperative Groups;
2. Large Academic Cooperative Groups;
3. Umbrella Networks of Cooperative Groups.

Regulatory autonomy and expertise constitute major differences between large and small academic groups which impact the models of partnership and are also the criteria for academic independence. While small, large and umbrella academic cooperative groups participate in commercial regulatory trials with the pharmaceutical industry (if the capability or resource can be provided), it is recognised that the more an academic group enforces principles of regulatory autonomy and independence, the more the group requires in-house expertise in regulatory and legal issues.

It is important for industry to keep in mind the particular capabilities of each category of academic cooperative group, what each can offer, as well as what they require within a collaboration. Here we also note that from the perspective of academia, it sometimes appears that there is a misunderstanding in confusing academia with contract research organisations (CROs). There is a consequent need for industry to explore how to partner with academia and engage them as an equal partner. Academia also points out, that industry's expectations for speed and rapidness need to conform to the purpose and the available resources.

Table 1 General categories of academic cooperative groups

Type of group	Example	Expertise	Clinical trial management	Resources
Small academic cooperative groups	Spanish Ovarian Cancer Research Group (GEICO)	Expertise in a particular disease area.	Generally, they need to engage a contract research organisation.	Small size limits resources. Geographically located in one or two countries with common regulatory and legal requirements. Limited number of sites. Phase II studies/limited number of patients.
Large academic cooperative groups	European Organisation for Research and Treatment of Cancer (EORTC)	Expertise in respective disease area available through a large network of investigators.	Possess in-house operational methodologies. Can transfer in-house data sets into regulatory dossiers. Pursue studies for secondary label indications at lower cost than industry sponsored clinical trials. Help with health technology assessment. ¹¹ Reduce duplication of efforts by coordinating group activities.	Multidisciplinary, international, expertise enables conduct of complex studies, for example, using biomarker section. Phase II or III studies. Large number of trial sites.
Umbrella networks of cooperative groups	Breast International Group (BIG)	Bring together experts and multiple cooperative groups, both small and large groups from many countries and from a particular field.	Dependent on resources of members. Reduce duplication of efforts through standardising processes among many small and large academic cooperative groups.	Take advantage of combined, international, resources of member cooperative groups. Conduct trials in rare diseases and/or in specific subtypes or subpopulations of patients. Phase II or III studies. Large number of trial sites.

TYPES OF CLINICAL TRIALS CONDUCTED BETWEEN INDUSTRY AND ACADEMIA: INDUSTRY SPONSORED CLINICAL TRIALS VERSUS INVESTIGATOR INITIATED TRIALS

The priorities used by academic cooperative groups and industry to manage their portfolios of work overlap considerably. Both are driven by prospects of important scientific advances and considerations of public health, including the health of patients with orphan diseases. Industry, of course, has to meet these needs to benefit its owners (often pension funds), while academic cooperative groups must manage within their annual budget. They do not consider concepts such as return on investment or the issue of ‘sustainability’ of the business in choosing how to invest, but prioritise merely by scientific/patient merit. This makes academic cooperative groups more willing to risk capital without a possibility of return, and hence they are more risk tolerant than industry when it comes to investing in novel ideas and science. However, from the industry perspective, it should be noted that industry makes a significant investment in science and novel ideas, especially in early research.

A general overview of the types of clinical trials conducted between industry and academia emphasising differences between industry sponsored clinical and investigator initiated trials (IITs) is provided in [table 2](#).

A recent change in the clinical trial landscape is, that regulatory approval may no longer be the most challenging obstacle. One can develop hundreds of checkpoint inhibitors, and several may receive European Medicines Agency (EMA) approval. The challenge has

shifted to access based on health technology assessment, societal and patient-centred aspects. This is where partnerships should be developed, because academic groups may be well-suited to meet societal agendas more than pure regulatory trial activities, which are needed, but no longer sufficient to obtain the widest possible access to innovative therapies.

In the academic clinical trial model, the Phase I/Ib trial is seen as a trial designed to learn. However, many Phase I/Ib trials are conducted outside of academic cooperative groups, because not all academic sites have the capability or expertise to conduct Phase Ib trials. This is a legitimate concern for industry. Furthermore, industry is generally reluctant to give a molecule to a broad range of sites, because the oversight needed to manage early drug development is generally handled by a selected number of sites with the experience to manage the unknown dosing and safety profile of a new medicine, which requires specialised operational capabilities and the ability to agree to standard contract terms to oversee drug development at this early stage of dose escalation and first in human trials. Here, industry would like to find additional ways to partner with academia in a cooperative group setting in order for the Phase Ib setting to work well.

Currently, industry often performs Phase I/Ib trials as pharma sponsored trials. However, to overcome this preference, cooperative groups would need to have a small network of sites that can provide the data and timelines needed for Phase I/Ib. It is worth noting, that industry does not necessarily want cooperative groups to shift

Table 2 Industry sponsored clinical trials versus investigator initiated trials

Industry-sponsored clinical trials	Investigator initiated trials
Designed to evaluate the efficacy and safety and often effectiveness of new drugs.	Often dedicated to questions on how to best use treatments.
Gain marketing authorisation and patient access for a new product, extend labelling for an approved product.	Can focus on patient-centric endpoints, for example, response rate.
Provide data for submission to health technology assessment (HTA) bodies.	Establish proof of concept for combination trials or exploratory studies.
Designed with the requirements of regulatory agencies in mind.	May seek to answer questions from the scientific community, regulators and/or payers for data that was not generated as part of the regulatory data provided under industry sponsored clinical trials.
Industry's research portfolios are generally segmented to include research and early development trials (Phase I First in Human and Phase II), product development trials (Phase Ib-III) and medical affairs studies (both post first-indication as well as pre-first indication supportive of filing studies, proof of concept studies and evidence generation for access/reimbursement purposes), all of which may include academic cooperative group studies.	Academia's research portfolios seek to increase knowledge and is centred on advancing patient care. Here, one can generally describe academic trials that are designed to learn followed by subsequent academic clinical trials designed to conclude.
See a marked need for Phase Ib trials (traditional Phase 1 trial is seen as a serial approach that adds time and cost to the development process).	Pragmatic clinical trials that test effectiveness of different therapy types in clinical practice. ¹²
Need to meet regulatory requirements for regulators globally in order to achieve drug approval and generate data to facilitate HTA review and patient access. The European Medicines Agency and many HTAs, for instance, accept well-established efficacy endpoints, and consequently, many industry-sponsored clinical trials use progression-free survival as the primary endpoint. ¹³	Can incorporate new endpoints (which are also a focus area of industry) to take advantage of advancing understanding of tumour biology, and these may include endpoints based on imaging, tumour kinetics, biological markers, quality of life and patient reported outcomes.
Concerned with the concept of sustainability, the ability to invest in research that will build new businesses that provide future revenue to sustain continued investment in research. Scientific advancement and satisfaction of unmet medical needs are required, but are not, on their own, sufficient to generate a sustainable research-driven business enterprise. An additional consideration for industry is the need to meet regulatory requirements for regulators globally in order to achieve drug approval and generate data to facilitate HTA review and patient access.	Decisions are made by volunteer members, are driven by the science, but also by the needs of the patients they see in daily practice. Investigators must be concerned with conducting research that is financially sustainable for themselves and the institutions they support, although they do not work primarily for profit.

their focus from Phase III to Phase I trials, rather they would like to more broadly see new models of collaboration in Phase I through III trials. Immune-oncology networks and other models of research will arise here with no cooperative group involvement, due in part to this gap in the cooperative group collaboration model with industry.

Here, it is important to recognise that the manner in which clinical trial evidence is being utilised to support industry registration programme has changed over the last decade. Classic drug development paradigms have moved from sequential Phase I, II, III studies and are being replaced by faster to market regulatory approval strategies. Indeed, the clinical trial landscape is continuously evolving, and recent advances such as those in omics-based capabilities, for example, are uncovering tremendous therapeutic opportunities.

EXAMPLES OF SUCCESSFUL COLLABORATIVE MODELS FOR ACADEMIA-INDUSTRY CLINICAL TRIALS

One might think, that complex infrastructure decreases agility during study set-up and conduct. However, in a forward-looking sense, an infrastructure which addresses and solves the bottlenecks, the trials you plug into it should benefit from that infrastructure, and, ultimately, bring agile clinical trial development. At the start, there can be long contractual negotiations, multiple additional guidance/working documents and decision-making needs to be aligned across team members/governance bodies and across the different partners of the study. From an industry perspective, working with one cooperative group can be vastly different than working with another cooperative group, because the internal rules of conduct differ significantly depending on the group, and even within a group depending on the type of collaboration model.

Table 3 Examples of successful collaborative models for academia-industry clinical trials

Trials	Type of trial	Description
HERA (NCT00045032), NSABP-B31/N9831 (NCT00004067, NCT00005970), and BCIRG006 (NCT00021255)	Randomised studies in the HER2(+) setting	Established changes in the standard of care for patients with HER2+ breast cancer while answering important questions for the scientific community. ^{14–23} Fast enrolment, valuable scientific input and medical expertise from both academia and industry. Benefitted from large network of sites and effective operational and scientific partnership with highly experienced study team members.
Vemurafenib (NCT01524978)	Basket trial conducted in patients with BRAF V600 mutation-positive cancers (solid tumours and multiple myeloma, except melanoma and papillary thyroid cancer). ²⁴	Assessed efficacy and safety of vemurafenib. Efficacy was seen in some but not other histologies. Regulatory approval for small biomarker defined populations can be achieved through this type of ‘basket’ trials
STAMPEDE (NCT00268476)	Umbrella trial assessed the effect of adding different agents to the standard of care for men starting long-term hormone therapy for metastatic or high-risk non-metastatic prostate cancer. ²⁵	Single histology, multiple biomarkers were each matched to treatments. Assessed effects of zoledronic acid, docetaxel or both (zoledronic acid showed no evidence of survival improvement; docetaxel chemotherapy, given at the time of long-term hormone therapy initiation, showed evidence of improved survival accompanied by an increase in adverse events). ²⁶ Trial was later amended to include assessment of abiraterone and enzalutamide, either alone or in combination, as well as radiotherapy for patients with newly-diagnosed metastatic disease.
EORTC trial 1559 (NCT03088059)	Phase II pilot study of personalised biomarker-based treatment strategy or immunotherapy in patients with recurrent/metastatic squamous cell carcinoma of the head and neck.	Based on potential biomarkers and molecular alterations identified in the biopsy from the central platform, patients were allocated to biomarker-positive patient cohorts and immunotherapy cohorts. Very efficient setup in practice, an almost disease specific infrastructure within an infrastructure, somewhat transparent to the investigator in the field. The network infrastructure is powerful, and the data can be used for further learning. Enabled study on patient population with an unmet medical need.

Cumbersome clinical trial operational systems can substantially hinder and add to the cost of drug development.² Thus, efforts should be directed towards re-engineering and simplifying current processes for trial pre-activation, activation and conduct, and, where possible, using central infrastructure and eliminating overlapping administrative and logistical requirements. Examples of successful collaborative models for academia-industry clinical trials are presented in [table 3](#).

One would imagine, that this is a similar experience for cooperative groups working with a variety of industry partners; some of the complexity is rooted in not knowing enough about how to work with the other entity and still come out with what you need for your trial or membership/independence. Partners need to learn and understand their roles during study set-up and conduct, understand what is, and what is not, negotiable, for example, what are industry’s needs for compliance with internal processes and regulatory requirements and what does academia need from a compliance/principles perspective. Finally, given the complex infrastructure, there needs to be stable team membership to ensure study-specific knowledge and experience are retained

and maintained and strengthened over the course of the study.

Industry feels that an area of potential improvement in collaboration within umbrella networks of cooperative groups would be to shift the discussion from a clinical trial-based approach to a disease area-based approach, aligning the model needs with the end use intended for the study data. Industry is very much ‘reactive’ to the investigator sponsored trial submission but would be open to larger discussions regarding development of drugs across a tumour type in different models aligned with the intended use of the study data. A challenge to such an approach is that different companies will not share their Clinical Development Plans with one another for competitive reasons, and perhaps combined with the knowledge that each academic group may submit its concept to one or more companies for support.

CURRENT CHALLENGES FOR ACADEMIA-INDUSTRY CLINICAL TRIALS IN EUROPE

The European Union (EU) Clinical Trials Regulation (EU CTR) was adopted by the Council of the European

Union and the European Parliament, applicable to all interventional trials, and published in the Official Journal of the European Union on 27 May 2014.³ It repeals Directive 2001/20/EC, which resulted in loss of competitiveness for European trialists and a reduction in trials of up to 25% since 2007 due to, among other reasons, an excess of bureaucratic requirements which were especially challenging for non-commercial cancer clinical trials.¹⁴

The EU CTR will go into effect when the new EU Clinical Trials Portal is completed by EMA. In the meantime, sponsors must comply with the EU Clinical Trials Directive (EU CTD) as implemented into national laws.

While implementing the EU CTD, several member states' national legislations made a distinction between commercial and non-commercial research and/or sponsors. This measure has helped a proportion of academic research to survive, but it also introduced a barrier that hinders private public partnerships.

From an industry perspective, the main challenge may arise in cases where these two types of trials produce results that the industry supporter decides, post facto, to use as a part of a commercial regulatory filing. Given the propensity of small, large and umbrella networks of cooperative groups to submit large Phase III studies to industry for supported studies, careful consideration must be applied by all parties involved regarding how countries and their sites interpret current legal framework.

With the upcoming implementation of the EU CTR, it is not yet known to which extent these elements of the national legislations will remain and still apply beyond the implementation of EU CTR.

Interpretation of the EU Clinical Trials Directive

The specific issue of most critical concern arises when a particular country's health authority interprets the EU CTD as to ensure that clinical trial data cannot be shared with industry from a study that was initially submitted as a non-commercial trial to the relevant national health authorities. This issue is compounded, when other EU countries' health authorities involved in the study interpret the EU CTD in a way that allows the clinical trial data to be shared with industry from a study that began as a non-commercial study. For a large multinational European academic cooperative group trial that involves sites from both of these types of countries in their studies, the impact is clear. Providing industry with the clinical trial data for only a percentage of the patients enrolled into the trial may cause industry to find this model of collaboration less attractive, particularly when the investment provides a positive clinical trial result for a Phase III study that cannot be used as part of a regulatory submission.

The impact on academic-clinical trials for some of these large academic multinational cooperative groups is, that their wishes to conduct large Phase III trials add a layer of complexity and risk to a company's decision on whether to collaborate on a large Phase III trial with the group in a supported study setting. Given the external market forces compelling companies to generate data quickly with fast

and efficient drug development, the practical impact may be a chilling effect on choosing a model of collaboration where the academic cooperative group cannot guarantee provision of data from all sites that wish to participate in a large Phase III study in a timely manner due to the disparate interpretations of the EU CTD within Europe.

However, industry-academia clinical trials still do move forward. From an industry perspective, the contract with the lead academic group for a clinical trial generally requests, that in the event that a clinical trial is positive and the company would like to use the data for a regulatory filing, the lead academic cooperative group must provide this data to industry. In many cases, there would then be a subsequent lump sum payment by industry to pay for the database, database cleaning and transfer to industry to meet the regulatory agencies requirements.

From the academic cooperative groups' perspective, the variable understanding of Ethics Committees (ECs), which are less touched by the EU CTD, also needs to be addressed, since this is an area of considerable risk and requires dialogue for clarity. For a commercial trial, the cost of standard of care, drug and other study-related activities are commonly covered by the commercial sponsor. This results in a higher per-patient cost, but the data can be used for commercial purposes.

A proposed novel solution would be for a third submission for non-commercial trial that has the potential to be used for commercial purposes in the correct circumstances, and agreeing in advance about what needs to be in place with ECs and regulators, for example, informed consent form (ICF) language, guarantees for money to be paid if the study is to be used in a filing, etc, in the event the non-commercial trial's data be used for commercial purposes. Lacking an additional model, there is the potential for a chilling effect for some EU countries that cannot offer assurances on the ability for industry to use the data for commercial purposes for a Phase III academic cooperative group trial.

A best practice proposal would be to segment, in advance, those countries that interpret clinical trial legislation to not allow sharing of data with industry for non-commercial trials to ensure that the considerations written above have been adequately described to them.

Finally, there is a lack of guidance concerning the implementation of the General Data Protection Regulation (GDPR), which creates difficulties for international collaborations in clinical research.^{5 6} GDPR must be viewed in light of the upcoming EU CTR, in vitro diagnostic regulations and medical devices regulations. The impact of these regulations on academic clinical research in Europe is still to be determined and should be discussed in greater depth between CAREFOR, industry and stakeholders interested in improving the opportunities for academic clinical research in Europe.

Commercial versus non-commercial intent

In investigator initiated trials (IITs), the regulatory sponsor is generally an investigator or an academic group,

whereas a pharmaceutical/biotechnology/medical device company is generally the sponsor of an industry clinical trial. While academic clinical trials are often considered to only encompass the former IITs, both models are used in collaboration with academic cooperative groups and have sought to answer key scientific questions from the oncology community.⁷

In general, a clinical trial is considered to have commercial intent when sponsored by a pharmaceutical manufacturer, has registration as intent and registration as an intent is included in the competent authority (CA) and EC submission for trial approval and in the ICF. Trials with non-commercial intent do not have registration as intent, so registration as an intent is not included in the ICF. However, these definitions have become blurred, because it is difficult to judge the intent of academic studies submitted with non-commercial intent which have gone on to provide data that substantially improves patient treatment outcomes and care. In these cases, pharmaceutical companies may want to have the ability to retrospectively file the data if allowed by regulators (CA) and ECs for the benefit of granting the widest access possible (ie, product labelling for an indication) to the new treatment for the benefit of patients with cancer.

Today, human biological materials (HBMs) and images are routinely collected during cancer clinical trials, and this component of the study is included in the ICF. Turning a trial to commercial intent means that the sponsor transparently informs the ECs of this use of the material and/or images. It is important to note the concept of a one-time consent in Article 28 (2) of the EU CTR, that allows data to be used beyond the end of a clinical trial for research purposes. The concept, now enshrined in EU law, will give patients the option, while enrolling for a clinical trial, to donate their data for research purposes beyond the end of a clinical trial (protected with strict ethical safeguards), bolstering research protection on clinical trial data.

COMMON LEGAL NEGOTIATION POINTS IN CONTRACTS FOR CLINICAL STUDIES

Given the different types of academic cooperative groups, clinical trials, as well as the variable models, regulations and complexities noted in this article to this point, there is a necessity for a clear contract between industry and academia to set the basis for the collaboration.

First, the contract should fully clarify the perspectives of each of the parties and ensure both parties have the same vision of their collaboration (ie, contract research organisation or equal partnership, the metrics to consider for evaluating the research).

Second, it should harmonise the different administrative/operational procedures and legal requirements of the parties, including timelines, costs and intellectual property (IP) rights. This part of contract negotiation can take a considerable amount of time, so it is advised that legal teams are involved early in the negotiations.

Finally, the advantages of the collaboration must be clearly set so as to demonstrate the positive aspects of the collaboration.

Mutual scientific interest is the driver for partnership, and operational requirements and contract definitions can play an important role in developing a sound contract. There are a number of points to consider when setting up a working agreement:

- ▶ Given the nature of academic groups, membership agreements and a master contract with each member site should be in place before the start of each study. Here, it should be permissible to share the site list.
- ▶ The intended use of the data and the timing of its use by industry should be clearly agreed to in the initial agreement.
- ▶ IP rights granted to industry include, at a minimum, 'Freedom to Operate' (FTO) with industry's Study Drug/Agent in the contract. FTO is the ability to perform a particular commercial activity (eg, commercialise a product, provide a service, perform a manufacturing process or use a product) without 'infringing' on the academic cooperative group, research sites or third party's valid IP rights. The rights in the contract to conduct the academic study with support and drug from industry should allow industry to have FTO for its Study Drug/Agent.
- ▶ There should be bi-directional points of contact and escalation for operational, financial and competitive considerations.
- ▶ The database structure and technical standardisation and licensing electronic data capture systems should be included.
- ▶ IP, inventions, data ownership/use rights, biomarker invention rights, confidentiality rights, etc, need to be agreed.
- ▶ The retrospective or prospective acquisition of database should be discussed and agreed in advance.
- ▶ Indemnity language needs to be included.
- ▶ Publication rights including a publication policy needs to be written and agreed to prior to the start of the study.
- ▶ It is also important to note, that the overall budget and budget rate cards should differ depending on type of trial.
- ▶ Access to the database during and after the conduct of the study should be clearly negotiated within the contract.
- ▶ Safety data reporting and quality agreements should be included within the contract (or as an addendum).

Budgeting and fair market value

Conducting an advanced international IIT in a fully developed professional environment and providing data readily acceptable by regulatory agencies globally compared with running a local study intended for publication only do not bear the same features and costs, but both types of trials can be run by academic cooperative groups as 'academic trials'.

Academic Cooperative Groups indicate, that industry often applies the same fair market value (FMV) reference to both scenarios, for which bench marking is not clear to academia, nor is it disclosed to them. Further, industry is not inclined to provide funds to a group or investigator beyond FMV, since this could be viewed as a 'kick-back' by law enforcement.⁸ Since some academic cooperative groups have sites in countries with different costs, providing a set cost across the board can create the perception that the drug company is inducing doctors to enrol patients in the trial by paying more than FMV for the test in that country. Industry needs to avoid even the smallest perception of impropriety at all costs, particularly when involving the provision of monetary or like-kind compensation to investigators, who also may prescribe their drugs. As a result, industry scrutinises the budgets to ensure they are FMV as a whole, but also in the loco-regional sense.

Delays are an oft-mentioned concern, and they might arise, for example, because of time contracting and reviewing study designs and budgets through international hierarchies or due to slow activation of the clinical trial. Therefore, a proposal for decreasing delays in start-up of clinical trials would be to create an intermediary focussed on improving operational capabilities, forming recommendations for database standards, data access alignment, contract terms and reviewing FMV for different study types should be considered. This intermediary would ideally comprise operational, legal, financial and medical individuals with both academic and industry experience in both academic and industry sponsored trials.

DATA ACCESS AND MANAGEMENT MODELS TO GOVERN THE FLOW OF INFORMATION AND DATA BETWEEN ACADEMIA AND INDUSTRY

Given the changes in classic drug development that are becoming increasingly evident, and these reflect, in part, the desire for new drugs to come to market for the benefit of cancer patients sooner, models that enable research to be conducted in pan-European collaboration with academia should consider addressing changes in how data is being utilised and the market forces at work, which may favour one model over another, in an effort to create fast and efficient drug development for the benefit of patients with cancer.

To begin, however, the clear distinction between data ownership and data access must be made. From an academic cooperative group perspective, nobody can own individual patient's data, but one can own the database. From an industry perspective, in standard IIT contract language, the cooperative group owns the data under an IIT, and this is achieved through its agreements with its cooperative group member institutions. So, for the purpose of this article, we speak about being the primary custodian of the data. The creator of the data is the custodian, and as the custodian, they have the responsibility

of seeing how it is shared and used, notably what rights can be granted to the data to third parties who supported the conduct of the study with both drug and funding. From the IIT sponsor's perspective, there are duties associated with being the custodian of the data, and the focus should be placed on the responsibilities associated with custodianship and on ensuring data access. From industry's perspective, support of trials is premised on the agreement of the IIT sponsor with sharing the data with industry in a particular format before the start of the trial (which can be as broad as sharing the publication of the trial results, or as focussed as sharing the raw clinical trial database and analyses databases).

The differences between HBM and data need to be recognised, apparent and described in the contract. HBM are a finite resource, whereas data is an infinite resource.

Academic cooperative groups acknowledge that there are circumstances, where the design of the study allows for an earlier look at the data (eg, interim analyses) without impacting the integrity of the primary endpoint. Earlier transfers of data can be requested and paid for if agreeable to both parties. The key, of course, is to not impact the integrity of the trial.

It should also be noted, that as soon as trial results are made public, industry, in the interest of patient safety and providing accurate replies to the doctors and healthcare providers worldwide, appreciates receiving the data at the earliest possible time point after the primary endpoint to (a) understand the data, (b) provide relevant updates to healthcare providers and (c) provide legally required information to investor relations per US Securities and Exchange Commission and other guidelines.

The data generated by academia can either serve registration purposes or be used for internal research by industry and the academic cooperative group. Depending on the aim of the data use, the conditions of access to the data can potentially change and the collaboration between industry and academia can differ.

The time point at which data can be shared must also be agreed. Academia stipulates that this be after completion of statistical analysis of the primary endpoint. Safety data can be shared earlier, as long as it does not interfere with the integrity of the analysis of the primary endpoint.

Retro-acquisition of the database from academia to industry is another consideration. Industry sometimes seeks to acquire the database of an academic study, and the conditions of this retro-acquisition of databases, and the potential consequences on the status of the academic study, need to be addressed.

Access to data by industry cannot always be included in the main research contract. Indeed, in many countries, granting industry access to data in the main contract prevents the recognition of academic research status. Consequently, academia and industry have usually relied on regulating this interaction post hoc following completion of a study, or, alternatively, have aimed to develop contract amendments. These amendments, however, bring additional difficulties in terms of administrative

burden and cost estimation. To be clear, the models of data acquisition are mapped to respect principles of independence as well as regulatory requirements. Whether the research is commercial or non-commercial must be declared, so changing status is possible, but the partners must abide by some rules. Moving forward, a best practice proposal would be to clarify, upfront, what these suggested rules may look like for the different types of clinical trials.

Right to use data for all legal purposes versus non-commercial purposes

For industry, the right to post hoc use of data needs to be clear. One also needs to consider that if not done fully when the trials are conducted, overall Good Clinical Practice compliance is hard to achieve retrospectively, if the trial data and information are to be used for regulatory approval purposes. So, having clarity on this upfront during contact discussions is very important.

For filing, industry requires a timeline and needs to make sure that the expectations are aligned at the start of the trial. This needs to be put into the terms of the contract. The cost of data cleaning, regulatory body costs, etc required for filing, and the previous experience of the academic group are important. As such, there is a need for the industry biometrics and monitoring teams to meet with academic teams. Currently, this type of meeting between industry and academic cooperative group biometrics and monitoring teams is underutilised in the eyes of industry, and there is room for improvement.

There are different models of data sharing, and a recent example is an agreement signed between GlaxoSmithKline and the EORTC for the transfer of HBM and clinical data collected as part of cancer immunotherapeutic research. Under the agreement, GlaxoSmithKline has provided EORTC access to all data and samples of the MAGRIT and DERMA negative studies, and these data comprise a tremendous source of research for academia.⁹

In their Requirements for Trials Between Academic Groups and industry, ENGOT proposes options for organising the clinical trial database.¹⁰ Under Option A, the database resides with the lead academic group. There is quality assurance and certified database software, audits by industry or industry assigned auditors and transfer of database to industry for registration issues and analysis. Under Option B, the lead academic group and industry agree on the choice of a CRO, the CRO is contracted by the lead academic group, and the database is located at the CRO. There is quality assurance and certified database software, audits by industry and by the lead academic group, if deemed necessary, installation of standard operating procedures for the respective protocol and information system for any violation to the sponsor, and transfer of the complete database to the lead academic group for scientific analysis and to industry for registration purposes. Finally, under Option C, the lead academic group and industry agree on the choice of a CRO, but here the CRO is contracted by industry, and

every transfer of the database for analysis must be granted by the leading academic group.

In some cases, especially in the case where there is registration potential, it is easier for umbrella cooperative groups to use CROs, since there is a great deal of variability in the ability of each member cooperative group in terms of data management, monitoring and drug safety reporting in each country.

EORTC holds that the integrity of the database be controlled by an independent group with a focus on the validity of the primary endpoint release, the statistical analysis and publication be independently processed and charters are drawn for the use of HBM. However, if the CRO holding the database is contracted for by industry, this would not meet EORTC's criteria for an academic study despite whether or not the actual transfer of the database to pharma must be granted by the lead academic group. This viewpoint difference between ENGOT and EORTC creates a heterogeneous environment for academic research in Europe. Industry believes that variations on the EORTC model are possible and exist today (eg, cooperative groups participating in pharmaceutical company sponsored trials where a CRO or the pharmaceutical company holds the database), and it is critical for advancement of the science for each party to be as collaborative as possible to move the field forward when there is a mutual scientific interest to pursue a clinical trial.

EMERGENCE OF NEW COLLABORATIVE MODELS

In the last 5 to 7 years, there has been an emergence of new collaborative models which could potentially accelerate academic research. These models are reacting to a complex clinical trial landscape, where the understanding of disease and treatment paradigms are evolving and changing at a faster pace in areas like immunoncology. There is a need to develop successful collaborations, including a sharing of data across networks, and these models are expanding on the self-imposed limits of previous models of collaboration in the interest of coming to answers more quickly and efficiently for patients with cancer. In addition to accelerating the generation and sharing of research data, there is also a high interest in new types of Real World Data sharing platforms. Table 4 presents examples of these new and emerging models outside of the current academic cooperative group networks.

CONCLUSION

This paper is a call to action to all communities in academia and industry that there is a need to examine, discuss and either clarify or improve on the way academia-industry research is being conducted. There are several drivers for change in academia-industry collaboration: collaboration and exchange of knowledge, streamlined contracting and agreements, bidirectional exchange of knowledge and exchange of samples and technology. The value of the collaboration can be maximised by focussing on strengths

Table 4 Presents examples of these new and emerging models outside of the current academic cooperative group networks

Collaborative model	Description
Innovative Medicines Initiative, a partnership between the European Commission and European Federation of Pharmaceutical Industry that connects academic and pharmaceutical industry research.	Projects cover components of the different steps of medicines development in several disease areas, and in cancer include BD4BO, CANCER-ID, EBISC, HARMONY, ITCC-P4 ITCC, MARCAR, Onco Track, PIONEER, PREDECT, and Quic-Concept ⁽²⁷⁾ .
BMS II-ON (International Immuno-Oncology Network)	International peer to peer collaboration (230 investigators, 13 different sites) to advance I-O science and translational medicine. Results thus far include Genetic Basis for PD-L1 Expression in Squamous Cell Carcinomas of the Cervix and Vulva ²⁸ , Intratumoral Balance between Metabolic and Immunologic Gene Expression Is Associated with Anti-PD-1 Response in Patients with Renal Cell Carcinoma ²⁹ , Intestinal microbiome analyses identify melanoma patients at risk for checkpoint-blockade-induced colitis ³⁰ , Combination Therapy with Anti-PD-1, Anti-TIM-3, and Focal Radiation Results in Regression of Murine Gliomas ³¹ , Interferon-Production by Peripheral Lymphocytes Predicts Survival of Tumor-Bearing Mice Receiving Dual PD-1/CTLA-4 Blockade ³² .
Roche imCORE (immunotherapy centres of research excellence)	Clinical research partnership comprising global network of basic and clinical scientists from 26 academic research institutions in cancer immunotherapy working with scientists from Roche and Genentech. Master agreements with the member sites, data sharing policies, central laboratory options for standardised biomarker research, etc have been implemented. Roche is working as one of the research institutions in collaboration with the network on existing and new investigational medicines, diagnostic technologies and emerging data. The network aims to identify and prioritise the most promising new treatment approaches.
Lung MAP (SWOG S1400, NCT02154490)	Collaboration across academia with multiple industry partners and advocacy groups in the United States. Multi-drug, multi-substudy, biomarker-driven squamous cell lung cancer clinical trial employing genomic profiling to match patients to substudies testing investigational treatments that may target the genomic alterations, or mutations, found to be driving the growth of their cancer ³³ . Patients are tested just once at enrolment according to a 'master protocol' and assigned to one of multiple trial substudies, each testing a different drug from a different pharmaceutical or biotechnology company. There is a shared information and infrastructure, better access for patients to promising drugs, better access for researchers to relevant enrollees based on genomic profiles, and less time and money needed before investigational drugs can be tested. A variety of pharmaceutical and biotechnology companies can participate in Lung MAP, each of which can test their treatment in a Lung MAP substudy.
IQNPath (International Quality Network for Pathology)	A harmonisation project serving as an example of how academia can partner to address scientific and clinical application questions in oncology. IQNPath is a multi-stakeholder forum for improving quality in tissue-based biomarker assessment, enables the exchange of expertise, coordination of interactions and sharing of benefits by developing value through joint workshops, trainings, tools and data resources, and it promotes external quality assessment/proficiency testing.
EORTC SPECTA	A pan-European screening programme to reach patients outside of clinical trials. It has a protocol for longitudinal collection of cancer patient data and human biological materials without immediate interventional intent, and it collects informed consent which allows future unspecified use of the collected data and human biological materials, provided that all undefined testing eventually obtains ethical committee approval (without repeat consent).

and mutual areas of interest, crafting a collaboration model and contract that is fit for the given purpose and focussing on programmes that provide meaningful scientific patient-centric advances that go beyond only competitive considerations.

Industry-wide analysis shows greater pressures for industry to move more quickly from first in man to patient access coupled with fast and efficient early development. This is the state of affairs for industry at a time when in areas like cancer immunotherapy more than

1000 different combinations were being tested in clinical trials in 2018. One impact of these external pressures is that industry and academia have evolved different types of collaboration models that were in place just 5 years ago.

From the perspective of industry, there are ways to create successful partnerships with academia. Specifically, there need to be:

- ▶ Dedicated responsibilities to act as liaisons at a portfolio level.
- ▶ Meetings need to be structured as opposed to ad hoc.

Box 1 Principles of interactions between the academia and industry

1. Clarify the roles and responsibilities of all partners involved in the study to generate a strong sense of belonging to a team.
2. Involve legal teams from an early stage, in order to draft a contract with a clear vision of the study reflecting the needs of both parties.
3. Acknowledge that data is an important output of the study and the creator of the data is its custodian bearing the responsibility concerning sharing it in the ultimate interest of the patient.
4. Agree on the intent of the trial prior to its start. If trial results indicate a societal/patient benefit bringing the study to registration, an agreement needs to be envisaged that meets both the requirements of industry and academic cooperative groups noting that some issues (eg, ICF language) may not be able to be obtained from 100% of the patients retrospectively, while other contract areas (eg, cost of data transfer) may be negotiated in later agreements subject to fair market value and other applicable regulations.

► Communication and vision need to be transparent and at least partially shared, for instance, not every successful collaboration needs to have three to four ongoing clinical trials. Some groups prefer one large trial which can take up to 18 months for study set-up, while other groups envisage a larger number of collaborations.

Moving forward, industry and academia need to work smarter together, new options of collaboration need to be discussed and established models need to be revisited.

Items introduced in this paper should continue to be discussed as separate matters (eg, GDPR, EU CTR, Models of Collaboration, Common Points of Contract Language Negotiation) and elaborated in separate articles in an effort to clarify understandings and improve the direction for academic clinical trials in the field of oncology in an era of fast paced global changes in clinical research environments.

Lastly, we propose principles of interaction (box 1) between the academia and industry which may provide guidance towards creating a clear and successful collaboration between both parties with the underlying premise that all clinical trials performed capture data of sufficient quality. Patients with cancer, who we serve, are counting on it.

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